DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of International Affairs
Washington, D.C. 20201

JUN 20 2002

Tokuo Yoshida
Quality Assurance and Safety: Medicines (QSM)
Essential Drugs and Medicines Policy (EDM)
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

Dear Mr. Yoshida:

I write in response to the request from the World Health Organization (WHO) for comments and information for the upcoming meeting of the WHO Expert Committee on Drug Dependence (ECDD). In particular, I refer to C.L.4.2002, which transmitted the WHO Questionnaire for Review of Dependence-Producing Psychoactive Substances by the Thirty-Third Expert Committee on Drug Dependence.

The enclosed information assembled by the U.S. Department of Health and Human Services (HHS) in response to your questionnaire is derived from many sources. In accordance with the Controlled Substances Act, the U.S. Food and Drug Administration (FDA) within HHS published the WHO notification and questionnaire on amfepramone (diethylpropion), amineptine, buprenorphine, delta-9-tetrahydrocannabinol, and tramadol in the *Federal Register* to solicit information. In response, the FDA received several comments relating to buprenorphine, delta-9-tetrahydrocannabinol, and tramadol. The FDA also received comments from four respondents regarding the adequacy of the WHO Questionnaire to provide sufficient data for assessing the abuse of these substances for the purpose of control under the international conventions. Please find enclosed all comments received in response to the *Federal Register* Notice. In addition, the enclosed information package includes information from the Drug Abuse Warning Network, the FDA's Adverse Event Reporting System, the U.S. Drug Enforcement Agency (DEA) National Forensic Laboratory Information System, and DEA's forensic laboratory database.

Also, we request, in accordance with the WHO Guidelines adopted in 1999, that the WHO forward to us the Critical Review Documents that will be developed for each of the substances under consideration by the ECDD, for our review and comment, well before the September ECDD meeting. We need to be able to offer our comments to the WHO on the Critical Review Documents, if necessary.

WHO QUESTIONNAIRE FOR REVIEW OF DEPENDENCE-PRODUCING PSYCHOACTIVE SUBSTANCES BY THE THIRTY-THIRD EXPERT COMMITTEE ON DRUG DEPENDENCE

COUNTRY NAME: United States of America

AGENCY NAME: U.S. Department of Health and Human Services

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The response should be mailed, faxed or e-mailed directly to:

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before ***17 May 2002***

If statistical information requested is not readily available, a brief descriptive answer would be appreciated.

Please attach copies of relevant study reports and other background information as appropriate.

If possible, answers in ***English*** *or* ***French*** *would be most appreciated.*

1. AMFEPRAMONE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product?

Yes. It is currently controlled in Schedule IV under the U.S. Controlled Substances Act (CSA) as a stimulant. It is available in the United States under the generic name, diethylpropion.

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

Trade names: Tenuate, Tenuate Dospan. Diethylpropion is also marketed in other products under the generic name diethylpropion.

Dosage forms: Available as a 25mg immediate release tablet and as a 75mg controlled release tablet.

Indications: Obesity: For the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of 30 kg/m^2 and who have not responded to appropriate weight reducing regimens (diet or exercise) alone. Diethylpropion is indicated for use as monotherapy only.

See attached product package insert under Tab C for additional information on Tenuate and Tenuate Dospan.

1.2 Is there other legitimate use of the substance? **No**

1.3 How is the substance supplied? (Imported/Manufactured in the country)

Diethylpropion is manufactured in the United States. In the past three years, there has been no importation of this substance but the United States has exported the following amounts to other countries:

Exports: 1999-2002

1999 101,414.374 grams primarily to Canada (101.4 kg)
2000 110, 365.850 grams primarily to Canada (110.3 kg)
2001 80, 738.714 grams primarily to Canada (80.7 kg)
2002 none so far this year (1/1/2002-5/1/2002)

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

U.S. data sources show little abuse of diethylpropion in the United States relative to similarly controlled weight control drug therapies. Between 1994

and 2000 there were 21 (unweighted) Emergency Department (ED) mentions involving amfepramone (reported as diethylpropion) in the DAWN[1] database. This number of ED mentions is considered very low relative to other substances in the DAWN database. The motive for these mentions was primarily suicide and not dependence and other psychic effects. Utilization of amfepramone (reported as diethylpropion) in the U.S. is low. The projected number of prescriptions (new and refill) of diethylpropion in 1997 was 531,000 and 379,000 in 2001.

[1] The Drug Abuse Warning Network (DAWN) system provides information on the health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED episodes). DAWN captures the non-medical use of a substance either for psychic effects, dependence, or suicide attempt. The nonmedical use of a substance captures the use of prescription drugs in a manner inconsistent with accepted medical practice; the use of over-the-counter drugs contrary to approved labeling; or the use of any substance for psychic effect, dependence or suicide. The ED data come from a representative sample of hospital emergency departments, which are weighted to produce national estimates. Many factors can influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening, whereas others may have sought care at the ED for detoxification because they needed certification before entering treatment. It is important to note that the variable "motive" applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables have been created.

2.2 If "yes", is the abuse increasing? (Yes/No/No information) **Not applicable.**

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

We are unaware of documented public health or social problems associated with the use of amfepramone (reported as diethylpropion).

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

The Drug Enforcement Administration (DEA) of the U.S. Department of Justice has several forensic laboratories throughout the United States that analyze drug evidence submitted by agents from seizures and street buys. Data from DEA's NFLIS[2] and STRIDE[3] data sources follows:

Data from NFLIS indicate that from 1999 through 2001, there were 75 exhibits of diethylpropion submitted to state/local forensic laboratories that participate

in NFLIS. The increase in the number of states with exhibits of this drug may be a reflection of new laboratories reporting to NFLIS. See Table 1 below.

Table 1. NFLIS DATA: Amfepramone (as Diethylpropion)

Year Submitted	Number of Exhibits/Cases	States
1999	26/24	AL,LA,TX
2000	21/19	AL, IA, MO, MS, SC, TX
2001	23/20	AL, FL, LA, MI, MO, MS, TX

STRIDE data indicate that over the past five years there has been a reduction in the amount of diethylpropion submitted as drug evidence to DEA laboratories for analysis. In addition, there have been fewer exhibits, cases and states submitting diethylpropion drug evidence in recent years. This data does not address diversion cases involving non-drug evidence, like prescription forgery or "doctor-shopping" activities. However, no DEA office has identified this drug as a primary drug of abuse/diversion in any state in the United States. See Table 2 below.

Table 2. STRIDE DATA: Amfepramone (as diethylpropion)

YEAR	EXHIBITS	CASES	TABLETS	LOCATION
1997	15	8	9,799	Texas, Florida, California, North Carolina
1998	18	5	367,378*	Texas, Tennessee, California
1999	16	11	1,373	Texas, Nevada, New Jersey, Georgia, Utah, Arizona, Tennessee
2000	4	2	222	Louisiana, Kansas
2001	6	3	48	Washington D.C., Louisiana, Florida

*** Includes a large seizure by DEA/Customs**

[2] National Forensic Laboratory Information System (NFLIS) is a DEA-sponsored project to systematically collect solid dosage drug analyses results from state and local forensic laboratories. Currently, 23 state laboratory systems and 26 local laboratories are reporting. This represents about 50 percent of all possible drug exhibits from state and local laboratories across the U.S. Data can not be trended as the number of laboratories reporting is increasing with time.

[3] System to Retrieve Information on Drug Evidence (STRIDE) is a database that maintains all drug analysis done by the U.S. DEA forensic chemists.

4. IMPACT OF TRANSFER TO A HIGHER SCHEDULE

4.1 If amfepramone is transferred to Schedule III of the Convention on Psychotropic Substances, do you think that its availability for medical use will be reduced?

No. This substance is already controlled in the United States. International control in Schedule III of the Psychotropic Convention would not require a change in the level of control of this substance in the U.S.

4.2 If "yes", would the reduction adversely affect the provision of medical care? (Yes/No/No opinion) **Not applicable**

2. AMINEPTINE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product?

No. This substance is not approved for marketing in the United States.

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

Not applicable

1.2 Is there other legitimate use of the substance? **No.**

1.3 How is the substance supplied? (Imported/Manufactured in the country)

Not applicable

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country?

No. The United States is not aware of documented information indicating abuse or misuse of amineptine in this country.

2.2 If "yes", any information on the extent of abuse? **No.**

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

The United States is not aware of documented evidence indicating public health or social problems associated with the abuse of amineptine in this country.

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

The United States is not aware of any illicit activity with this substance in the United States.

4. IMPACT OF SCHEDULING

4.1 If amineptine is placed under international control, do you think that its availability for medical use will be reduced? **No.**

4.2 If “yes”, would the reduction adversely affect the provision of medical care? (Yes/No/No opinion) **Not applicable.**

3. BUPRENORPHINE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No)

Yes. Buprenorphine was approved for medical use as a parenteral analgesic product and was rescheduled from Schedule II to Schedule V of the CSA in 1985. As a derivative of opium (thebaine), buprenorphine is controlled as a narcotic. This scheduling activity preceded the addition of buprenorphine to Schedule III of the Convention on Psychotropic Substances, in 1989, which the U.S. Government voted to support.

In the U.S. Federal Register of March 21, 2002 (67 FR 13114), the DEA published a proposed rule to increase the regulatory controls placed on buprenorphine by rescheduling buprenorphine from a Schedule V narcotic to a Schedule III narcotic. This proposal was not based upon an escalation in the abuse of buprenorphine, but based upon the anticipated approval of new dosage forms with different relative abuse potential profiles.

The DEA proposal followed the review and consideration of a recommendation from the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (DHHS). Neither FDA nor DEA recommended applying the same level of control to buprenorphine that is applied to heroin, morphine, oxycodone, codeine, methadone, propoxyphene, or other full opioid agonists.

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

Trade name(s): Buprenorphine is approved for marketing in the United States in an injectable formulation under the trade name Buprenex. Buprenorphine is also marketed as a generic product.

Dosage form(s): Injectable, 0.3 mg/ml, 1 ml/ampule

Indication(s): Approved indication for the marketed product is for the relief of moderate to severe pain.

See attached product package insert under Tab E for additional information on Buprenex.

1.2 Is there other legitimate use of the substance? (No/Yes, it is used for …….)

In addition to the currently marketed product, several New Drug Applications for buprenorphine-containing products are currently under review by the FDA. Among these applications are Subutex (sublingual buprenorphine single entity) 2 mg and 8 mg strength tablets and Suboxone (sublingual

buprenorphine/naloxone combination) 2mg: 0.5mg and 8mg: 2mg strength tablets. Both products are being developed for use in the treatment of opiate addiction. These products are different from the current approved buprenorphine product, Buprenex, in terms of the concentration of the active component, dosage form, indication and target population. Buprenex is an injectable that contains 0.3 mg of buprenorphine per ml (a low concentration compared to the oral products under development) and is indicated for the relief of moderate to severe pain.

Subutex and Suboxone have been extensively studied for use in the treatment of narcotic addiction as replacement therapy. The New Drug Applications (NDAs) for these products for the treatment of opiate addiction, under review at the FDA, have been determined by FDA to be "approvable", which means that the application or abbreviated application will be approved if specific additional information or material is submitted or specific conditions are agreed to by the applicant (21 Code of Federal Regulations Part 314.110).

Currently, agonist pharmacotherapy for the treatment of opiate dependence consists of dispensing methadone and LAAM in U.S. Government approved clinic settings. Physicians are not allowed to prescribe opiates, except under special circumstances recently specified by the U.S. Congress, for the treatment of opiate dependence. The U.S. Congress enacted legislation in 2000 to reduce the demand for illicit opiates by increasing the capacity for opiate addiction treatment. The new legislation, together with potential opioid treatment medications such as buprenorphine, is intended to expand opiate addiction treatment to underserved populations by enabling qualified physicians to prescribe Schedule III-V approved opiates in a form of office-based treatment. The DHHS' Substance Abuse and Mental Health Services Administration (SAMHSA) has trained approximately 1,500 physicians to be eligible to prescribe certain opioid treatment medications (such as buprenorphine) for the detoxification or maintenance treatment of up to 30 patients. Additionally, physicians who are board certified in an addiction subspeciality will also be eligible to prescribe these products for opiate dependence treatment.

In the United States, there is currently a "treatment gap" of approximately 700,000 persons who are unable to receive treatment for their opiate addiction. A major goal of the U. S. Government is to expand treatment to reduce this gap. Buprenorphine is currently viewed as a treatment that could help realize this goal.

Buprenorphine, in office-based settings, could also help to address the problem that many younger opiate dependent individuals seeking treatment do not have access to methadone programs, are reluctant to enter programs, and are unsuited to them, and unnecessarily continue to use opiates as a result.

1.3 How is the substance supplied? (Imported/Manufactured in the country)

Buprenorphine is not manufactured in the United States. The following table provides information regarding the amounts of buprenorphine imported into the United States in recent years.

YEAR	AMOUNTS IMPORTED GRAMS	COUNTRY * PRIMARY EXPORTER
1999	5,638.659	UK*, NET, NZE,
2000	9,969.716	AUL, NET, UK, GER*
2001	15,366.67	NET, CZE, GER*, UK
Jan-April 2002	2,150	UK, AUL*

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

Little abuse of the currently marketed product, Buprenex, has been documented in the United States. Buprenorphine does not appear in the top 50 drugs identified in the "Estimated number of emergency department drug episodes, drug mentions, mentions of selected drugs, and total visits for total coterminous U.S. by year: 1993-2000" (Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2000 (03/2001 update). Between 1994 and 2000, there were 17 (unweighted) buprenorphine-related ED mentions in DAWN[1]. This is considered a very low number of ED mentions relative to other substances in the DAWN database.

[1] The Drug Abuse Warning Network (DAWN) system provides information on the health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED episodes). DAWN captures the non-medical use of a substance either for psychic effects, dependence, or suicide attempt. The nonmedical use of a substance captures the use of prescription drugs in a manner inconsistent with accepted medical practice; the use of over-the-counter drugs contrary to approved labeling; or the use of any substance for psychic effect, dependence or suicide. The ED data come from a representative sample of hospital emergency departments, which are weighted to produce national estimates. Many factors can influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening, whereas others may have sought care at the ED for detoxification because they needed certification before entering treatment. It is important to note that the variable "motive" applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables have been created.

2.3 If "yes", is the abuse increasing? (Yes/No/No information) **No. However as mentioned above in 1.2, several new dosage forms for buprenorphine are under development. If these are approved for marketing in the United States, it is**

anticipated that the availability of buprenorphine will increase. Past experience in the United States suggests that the introduction of new opiate drug products increase drug availability, which may result in increased abuse and/or diversion.

2.4 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

The United States is not aware of significant public health or social problems associated with the use of the currently marketed product, Buprenex.

As described above in question 1.2, two New Drug Applications (NDA) are under review at the FDA. Once the high-dose sublingual buprenorphine products are available and prescribed in the opiate-dependent population, it is anticipated that the United States will experience abuse and diversion of these products, similar to that observed in other countries where high dose buprenorphine tablets have been marketed for the same indication. The DEA and the DHHS completed reviews of relevant data from both domestic and foreign sources as part of a medical and scientific reevaluation of buprenorphine's status under the Controlled Substances Act. The DHHS evaluation, entitled "Buprenorphine: Recommendation to Reschedule Buprenorphine From Schedule V to Schedule III of the Controlled Substances Act", includes information on the extent of public health and social problems associated with the abuse of buprenorphine tablets. The DEA review, entitled, "Buprenorphine: DEA Review Document Scheduling under the CSA February 2002"also includes information on the risk to the public health. (See attached FDA review under Tab M and attached DEA review under Tab N).

The National Institute on Drug Abuse (NIDA), National Institutes of Health of DHHS, submitted safety and drug abuse information from its U.S. clinical trials of buprenorphine. Three overdose cases observed in clinical trials were described as accidental overdose and resolved without sequelae. NIDA also reported the death of a subject enrolled in a clinical trial. The coroner ruled the death to be due to accidental benzodiazepine toxicity. (See complete information from NIDA attached under Tab L).

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

There is no evidence of clandestine manufacture of buprenorphine in the United States. In addition, forensic laboratory data from the DEA's STRIDE[2] database show very few seizures of buprenorphine injectable submitted to the United States DEA for analysis. Since 1997, there have been 20 exhibits consisting of 605 ampules and 677 tablets, most of which were seized by the U.S. Border Patrol. State/local forensic laboratory data obtained from the

NFLIS[3] from 1/1997 to 12/2001 show 23 exhibits from five different states. According to the DEA, these data reflect both the limited prescription of buprenorphine injectable and the low priority that law enforcement personnel place on lower schedule pharmaceuticals.

NIDA indicates that there have been some anecdotal reports of diversion occurring in clinical trials.

[2] System to Retrieve Information on Drug Evidence (STRIDE) is a database that maintains all drug analysis done by the DEA forensic chemists.

[3] NFLIS is a DEA-sponsored project to systematically collect solid dosage drug analyses results from state and local forensic laboratories. Currently, 23 state laboratory systems and 26 local laboratories are reporting. This represents about 50 percent of all possible drug exhibits from state and local laboratories across the United States. Data cannot be trended as the number of laboratories reporting is increasing with time.

4. IMPACT OF TRANSFER TO SCHEDULE I/II OF THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961, ON MEDICAL AVAILABILITY

4.1 If buprenorphine is transferred from Schedule III of the Convention on Psychotropic Substances to either Schedule I or II of the Single Convention on Narcotic Drugs, do you think that its availability for medical use will be reduced? (Yes/No/No opinion)

See 4.2 below

4.2 If "yes", would the reduction adversely affect the provision of medical care? (Yes/No/No opinion)

Marketed product: Buprenorphine is marketed in the United States as a parenteral, injectable solution containing 0.3 mg of buprenorphine per ml for the relief of moderate to severe pain. There is no evidence to suggest that parenteral buprenorphine availability for medical use would be reduced if buprenorphine were moved from Schedule III of the Convention on Psychotropic Substances to Schedule I or Schedule II of the Single Convention on Narcotic Drugs.

Products pending approval: Several HHS agencies and outside parties have expressed the concern that were buprenorphine to be rescheduled under the Single Convention on Narcotic Drugs (Schedule I or II), buprenorphine drug products in the United States would be placed in Schedule II of the CSA. Because the Drug Abuse Treatment Act of 2000 (U.S. Public Law 106-310) permits the office-based treatment of opiate addiction with opiates in Schedules III-V, but not of CII opiate agonists, the buprenorphine products pending

approval for opiate addiction would potentially be less available. In particular, NIDA has expressed concern that moving buprenorphine to Schedule I or II of the Single Convention may limit buprenorphine availability for physicians and pharmacies resulting in an adverse effect on medical care in the United States. NIDA provided information in support of their concerns. (See complete information from NIDA attached under Tab L).

However, the DEA, which bears statutory authority to implement and enforce the CSA, provided the following comments: "Should buprenorphine be placed in Schedule I or II of the Single Convention, the U.S. would need to place bulk buprenorphine in Schedule II of the CSA. However, products of buprenorphine would not require Schedule II control. The DEA recently published a proposed rule to place all buprenorphine products in Schedule III of the CSA (See attached DEA review under Tab N and attached Federal Register Notice of proposed rule under Tab O). This proposed placement for buprenorphine products (Schedule III narcotic) would be sufficient to meet the requirements of Schedule I or II controls under the Single Convention. It is DEA's view that this action would not adversely affect the availability of buprenorphine for medical use in the United States especially in regard to the use of buprenorphine for narcotic treatment in accordance with the Drug Addiction Treatment Act (DATA, 21 U.S.C. 823)."

Comments on Impact of rescheduling under the Single Convention from Outside Parties: Attached are comments from two law firms, Tab J (Hyman, Phelps, and McNamara) and Tab K (Hogan and Hartson) that were submitted in response to the Federal Register Notice on the WHO Questionnaire.

4. *DELTA*-9-TETRAHYDROCANNABINOL[1]

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product?

Yes. The FDA-approved tetrahydrocannabinol (THC)-containing product is controlled in Schedule III of the U.S. Controlled Substances Act (CSA). All other forms of the substance, delta-9-THC, and all other cannabinoids have no currently accepted medical use in the U.S. and are controlled in Schedule I of the CSA.

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

Trade name: Marinol (dronabinol)

Dosage forms and strengths: Marinol containing synthetic delta-9-tetrahydrocannabinol (delta-9-THC) in sesame oil is available as 2.5mg, 5mg, and 10mg gelatin capsules.

Indications: Dronabinol is currently approved for marketing for the treatment of anorexia associated with weight loss in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy.

See attached product package insert under Tab D for more information on Marinol.

1.2 If the answer to 1.1 is "no", is there other legitimate use of the substance? (Yes/No)

See 1.1 above

1.3 If "yes", please describe the purpose of use.

See 1.1 above.

1.4 If there is legitimate use of the substance, how is the substance supplied? (Imported/Manufactured in the country)

Synthetic Delta-9-THC (dronabinol) and Marinol are manufactured in the United States.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No)

[1] dronabinol

In the United States, there is little documented abuse/diversion of the THC-containing product, Marinol. Between 1994 and 2000, there were 30 (unweighted) dronabinol-related ED mentions in DAWN[2]. These numbers are considered very low relative to other substances in the DAWN database.

The FDA Adverse Event Reporting System (AERS[3]) contains no reports of abuse or misuse of the marketed product, Marinol.

[2] The Drug Abuse Warning Network (DAWN) system provides information on the health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED episodes). DAWN captures the non-medical use of a substance either for psychic effects, dependence, or suicide attempt. The nonmedical use of a substance captures the use of prescription drugs in a manner inconsistent with accepted medical practice; the use of over-the-counter drugs contrary to approved labeling; or the use of any substance for psychic effect, dependence or suicide. The ED data come from a representative sample of hospital emergency departments, which are weighted to produce national estimates. Many factors can influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening, whereas others may have sought care at the ED for detoxification because they needed certification before entering treatment. It is important to note that the variable "Motive" applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables have been created.

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA receives adverse drug reaction reports from manufacturers as required by regulation. Health care professionals and consumers send reports voluntarily. These reports become part of a database. The structure of this database is in compliance with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation.

2.2 If "yes", any information on the extent of abuse?

<u>Comments from Hurley and Associates, authorized representatives for UNIMED Pharmaceuticals</u>: Comments were submitted in response to the Federal Register Notice on the WHO Questionnaire. Hurley states that the American Association of Poison Control Centers (AAPCC) reported six total cases of intentional exposure to Marinol during the period 1992-1994, with three of these being abuse. They also report that a search of the UNIMED Pharmaceuticals safety database did not reveal any signals of Marinol abuse. (See complete text of comments from Hurley and Associates attached under Tab H).

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

The United States is not aware of public health or social problems associated with the use of the marketed product, Marinol.

Comments from Hurley and Associates authorized representatives for UNIMED Pharmaceuticals: Comments were submitted in response to the Federal Register Notice on the WHO Questionnaire. Dr. Hurley states that a search of the DAWN database demonstrated that from 1988 to 1994 there were no ED episodes of dronabinol reported. (See complete text of comments from Hurley and Associates attached under Tab H).

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

The U.S. has very little data to indicate diversion of the U.S. marketed product Marinol. Since 1998, only 12 exhibits have been analyzed in state/local forensic laboratories that participate in the NFLIS[4]. Since 1997, there were only nine exhibits for synthetic THC in the DEA forensic laboratory database, STRIDE[5].

[4] National Forensic Laboratory Information System (NFLIS) is a DEA-sponsored project to systematically collect solid dosage drug analyses results from state and local forensic laboratories. Currently, 23 state laboratory systems and 26 local laboratories are reporting. This represents about 50 percent of all possible drug exhibits from state and local laboratories across the U.S. Data can not be trended as the number of laboratories reporting is increasing with time.

[5] System to Retrieve Information on Drug Evidence (STRIDE) is a database that maintains all drug analysis done by the U.S. DEA forensic chemists.

5. TRAMADOL (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No) **Yes.**

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

Trade name(s): Tramadol is available for marketing in the United States under the trade name Ultram. Tramadol in combination with acetaminophen is marketed as Ultracet.

Dosage form(s): Ultram (50 mg tramadol hydrochloride oral tablets) and as Ultracet (37.5 mg tramadol hydrochloride and 325 mg acetaminophen oral tablets).

Indication(s): Tramadol is indicated for the treatment of moderate to moderately severe pain.

See attached product package insert labeling under Tab F for more information on Ultram and Ultracet.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

DEA data show diversion of, and an active illicit market for tramadol. Abuse in the United States has been reported in substance abusers, chronic pain patients, and health care professionals. Large numbers of adverse drug events of U.S. origin have been reported to the FDA between March 3, 1995 (date of approval) and October 31, 2001: there have been 518 reports of "Drug Abuse," 317 reports of "Drug Dependence," 14 reports of "Increased Tolerance," and 628 reports of "Withdrawal Syndrome."

The DAWN[1] annually reports the estimated number of drug mentions associated with abuse in a sample of hospital emergency departments (ED) in 21 metropolitan areas. The most common reason for DAWN ED mentions related to tramadol has been "drug overdose." Tramadol is currently marketed as a non-scheduled analgesic, and its opiate properties are attributed primarily to the M1 active metabolite.

DAWN ED mentions for tramadol are: 1,418 (1997), 1,972 (1998), 1,113 (1999), 1,810 (2000), and 1,219 (January-June 2001). Adjusting for drug availability as measured by number of prescriptions for tramadol (IMS HEALTH, National Prescription Audit), the percentage of ED mentions relative to number of prescriptions (from 1997 through June 2001) was 1.46%. For a comparator, codeine, the ED mentions relative to prescriptions was 1.55%; for the

comparator, dextropropoxyphene, the ED mentions relative to prescriptions was 1.86%. The majority of ED mentions for tramadol in combination with other substances involved the following: alcohol, acetaminophen, amitriptyline, cyclobenzaprine, carisoprodol, hydrocodone, oxycodone, cannabis, cocaine, sertraline, clonazepam, alprazolam, and zolpidem.

Table 1 (below) contains data from IMS HEALTH, National Prescription Audit *Plus*™ and projected total number of prescriptions (new and refill) dispensed by U.S. retail pharmacies (chain, independent, food stores) including mail order and long-term care facilities in the U.S.

Table 1. Drug Utilization Values Reported as Annual Prescriptions dispensed in the U.S.A. (In Thousands) For Tramadol, Propoxyphene, Codeine and Hydrocodone

DRUGS	PROJECTED TOTAL PRESCRIPTIONS [a]				
	1997	1998	1999	2000	2001
TRAMADOL	10,425	11,012	11,631	12,044	13,075
PROPOXYPHENE	31,589	31,951	31,547	30,992	30,404
CODEINE	40,603	39,318	40,811	37,362	36,458
HYDROCODONE	63,626	71,020	81,725	88,778	96,318

[a] Source: IMS HEALTH; National Prescription Audit *Plus*™

[1]The Drug Abuse Warning Network (DAWN) system provides information on the health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED episodes). DAWN captures the non-medical use of a substance either for psychic effects, dependence, or suicide attempt. The nonmedical use of a substance captures the use of prescription drugs in a manner inconsistent with accepted medical practice; the use of over-the-counter drugs contrary to approved labeling; or the use of any substance for psychic effect, dependence or suicide. The ED data come from a representative sample of hospital emergency departments which, are weighted to produce national estimates. Many factors can influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening, whereas others may have sought care at the ED for detoxification because they needed certification before entering treatment. It is important to note that the variable "motive" applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables have been created.

The DAWN Medical Examiner (ME) component provides information on the consequences of drug use in selected areas of the United States as manifested by drug-induced or drug-related deaths reported by participating medical examiners and coroners. The ME's data do not come from a representative sample of medical examiner offices and cannot be used to produce national

estimates of the number of drug-related deaths. Because some ME's stop sending data and others are continuously being recruited into the system, the number of ME's changes from year to year. To produce trends, DAWN formed a consistent panel of ME's who have been reporting consistently (at least 10 months of each year in question) over the time period of interest.

A medical examiner report to DAWN may have multiple drug mentions. Up to six different substances, in addition to alcohol in combination, can be recorded for each reportable case. As a result, although the cause and manner of death is associated with each drug reported to DAWN, not every reported substance is by itself, the cause of death. To be reported to DAWN the death should have been drug-induced or drug-related; involved an illegal drug or non-medical use of a legal drug; and the reason for taking the substance should have been for psychic effect, dependence, or suicide.

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

From March 1995 (date of U.S. marketing approval) through December 2001, 455 unduplicated cases of death in association with tramadol hydrochloride use were reported to the FDA. During this time period, approximately 70 million ULTRAM prescriptions were dispensed in the United States. The FDA's Office of Drug Safety, Center for Drug Evaluation and Research conducted two reviews of the deaths associated with tramadol.

The first FDA review, dated April 21, 2000, describes 322 deaths associated with the use of tramadol between March 1995 and March 2000. One hundred and sixty-three of these originated from the U.S.; 68 reports did not include identification of country of origin. Ninety-five deaths (29.5 percent) were coded under the terms, intentional overdose and unintentional overdose. There were 56 intentional overdose cases, of which 40 cases involved single or multiple drug overdose and 16 cases involved drug abuse and dependence. One patient was the victim of malicious intent.

Findings from a subsequent FDA review dated January 23, 2002 were consistent with those of the earlier review. From March 2000 to January 2002, 133 deaths were reported. Of these, 29 were not of U.S. origin, 89 were from the U.S., and 15 were of unknown origin. Twenty were reported as completed suicide, 17 as overdose, and 9 as non-accidental overdose.

A second source of mortality data is the DAWN ME reports. Mortality data from DAWN provide information on drug-induced and drug-related deaths identified and submitted by participating jurisdictions across the United States. The drug abuse deaths do not represent the United States as a whole, nor do they necessarily represent the total number of deaths in which drug abuse was a causal or contributing factor. Rather, DAWN cases reflect the number of drug abuse deaths reviewed, identified, and reported by participating medical examiners and coroners in selected metropolitan areas.

There were 298 DAWN ME reports for tramadol from 1997 to 2000. Of these, 17 involved tramadol alone and 281 involved tramadol taken in combination with other substances. The other substances included alcohol, acetaminophen, amitriptyline, cocaine, morphine, oxycodone, and dextropropoxyphene. To adjust the ME reports for drug utilization, prescription data (IMS HEALTH, National Prescription Audit) were used as the denominators. From 1997 through 2000, one death for every 125,000-tramadol prescriptions was reported. For the comparator, dextropropoxyphene, there was one death for every 73,000 prescriptions reported to DAWN, and one death for every 192,000 prescriptions for hydrocodone.

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

According to the DEA, approximately 70 cities across the United States have DEA offices with diversion investigators assigned to them. Reports are submitted by these offices to DEA headquarters on a quarterly basis. Included in the reports is intelligence information regarding use/abuse/diversion of common drugs of abuse, new drugs of abuse, and, if available, street prices for these substances. For the most part, the drugs reported are legitimate pharmaceuticals. The source of data are investigations conducted by DEA and information provided by state and local police and regulatory agencies.

According to DEA field office reports (1997-2001), tramadol is the second most cited commonly abused/diverted non-controlled substance in the United States. According to 2001 quarterly reports from DEA field offices, tramadol is considered a problem in 17 states. In 2001, three offices reported street prices for ULTRAM ranging from $2.00 to $4.00 per tablet. DEA offices in Minnesota, New Mexico and Louisiana reported that ULTRAM is a popular drug of abuse among medical professionals.

Data from state/local forensic laboratories that participate in the NFLIS[2] show 247 exhibits of tramadol from January 1997 through December 2001: 6 in 1997, 12 in 1998, 46 in 1999, 71 in 2000 and 111 in 2001. In 2000 and 2001, there were only seven exhibits in STRIDE[3]. As tramadol is an uncontrolled substance federally and in most states, laboratory submissions are not a good barometer of the extent of illicit activities with this substance.

[2] National Forensic Laboratory Information System (NFLIS) is a DEA-sponsored project to systematically collect solid dosage drug analyses results from state and local forensic laboratories. Currently, 23 state laboratory systems and 26 local laboratories are reporting. This represents about 50 percent of all possible drug exhibits from state and local laboratories across the United States. Data cannot be trended as the number of laboratories reporting is increasing with time.

[3] System to Retrieve Information on Drug Evidence (STRIDE) is a database that maintains all drug analysis done by the U.S. DEA forensic chemists.

4. IMPACT OF SCHEDULING

4.1 If tramadol is placed under international control, do you think that its availability for medical use will be reduced? (Yes/No/No opinion)

No. We are not aware of evidence that international scheduling of tramadol would reduce its availability for legitimate medical use in the United States. Should tramadol be controlled internationally, the DEA would place tramadol under an appropriate level of control in the United States. Control under the CSA does not alter the availability of drugs for legitimate medical purposes.

4.2 If "yes", would the reduction adversely affect the provision of medical care? (Yes/No/No opinion) **Not applicable**

Please elaborate: **Not applicable**

Comments from Pharmaceutical Research and Manufacturers of America (PhRMA) including Declaration from Frank L. Hurley, Ph.D: Comments were submitted in response to the Federal Register Notice on the WHO Questionnaire. Summarizing, these comments provide information and analysis regarding the validity of the WHO questionnaire. Please note that Item (7) on page 4 of Dr. Hurley's declaration is not a correct presentation of item 5.4.1 and 5.4.2 in the WHO questionnaire regarding tramadol. (See complete comment from PhRMA attached under Tab G).

Comments from Hyman, Phelps & McNamara on behalf of Johnson and Johnson: Comments submitted in response to the Federal Register Notice on the WHO Questionnaire provide information on tramadol abuse risk and information regarding adequacy of the WHO Questionnaire in assessing abuse, illicit activity, and the impact of international control. The respondent states that tramadol demonstrates a low abuse liability and a low risk for development of tolerance and psychological or physical dependence. In comparison with morphine, withdrawal is mild to moderate in intensity. Information on the international control status of tramadol is presented. In 26 of the 104 countries where available, tramadol is subject to psychotropic drug scheduling. Tramadol is a narcotic in three countries (with codeine-like status in two countries). The drug is unscheduled in the remaining countries. No reviewable data were presented in support of the respondent's view that scheduling adversely effects the provision of medical care in the United States. (See complete comments from Hyman, Phelps & McNamara attached under Tab I).

6/20